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Single use versus reusable catheters in intermittent CatheterizatiOn for treatment of urinary retention: a protocol for a Multicenter, Prospective, RandomizEd controlled, non-inferiority trial (COMPaRE)

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Abstract

Introduction: Chronic urinary retention is a common lower urinary tract disorder, mostly neurogenic or idiopathic in origin. The preferred treatment is clean intermittent urinary self-catheterization (CISC) four to six times a day. In most European countries, virtually all patients use single use catheters, which is in contrast to several countries where the use of reusable catheters is more common. The available literature on the use of reusable catheters is conflicting and until now, no randomized controlled trial with sufficient power is performed to investigate if reusable catheters for CISC is as safe and effective in comparison to single use catheters.

Methods and analysis: We described this protocol for a prospective, randomized-controlled non-inferiority trial to investigate if the use of a reusable catheter is as safe and effective as a single use catheter for CISC patients, measured by symptomatic urinary tract infections (sUTIs). Secondary objectives are adverse events due to a sUTI, urethral damage, stone formation, quality of life and patient satisfaction. A cost-effectiveness analysis will also be performed. 456 Participants will be randomized into two groups stratified for age, gender, menopausal status and (non-)neurogenic underlying disorder. The intervention group will replace the reusable catheter set every two weeks for a new set and replace the cleaning solution every 24 hours. The control group continues to use its own catheters. The primary outcome (amount of sUTIs from baseline to one year) will be tested for non-inferiority. Categorical outcome measures will be analysed using Chi-square tests and quantitative outcome variables by t-tests or Mann-Whitney U tests. Two-sides p values will be calculated.

Ethics and dissemination: This protocol was reviewed and approved by the Medical Ethics Committee of the Erasmus MC (MEC 2019-0134) and will be performed according to the CONSORT checklist for non-inferiority trials.

Trial registration: Nederlands Trial Register; NL8296 (https://www.trialregister.nl/trial/8296)

Article summary

Strength and limitations of this study:

- This protocol describes a prospective, randomized-controlled, non-inferiority study and will provide information regarding the safety, effectiveness, patient satisfaction and costs-effectiveness of reusable catheters in comparison to single use catheters in patients on CISC of the urinary bladder.
- It is the first study protocol with a sufficient sample size calculation able to detect non-inferiority for the reusable catheter measured by sUTIs.
- The definition of a sUTI is fully and clearly defined in this protocol
- The reusable catheter set is more time consuming what might result in a higher dropout rate in the intervention arm
- Non-inferiority of the reusable catheter will lead to the following implications: increased patients choice and reducing fear of running out of catheters, a reduction in health care costs and plastic medical waste and the opportunity for patients in low income countries to perform CISC with a reusable catheter as the single use catheter at present is much too expensive for the health care systems in low income countries.

Keywords: clean intermittent catheterization, urinary retention, underactive bladder, single use catheters, reusable catheters, randomized controlled trial, non-inferiority trial

Background

Millions of people have difficulty in emptying their urinary bladder resulting in urinary retention or clinically significant post void residue (PVR) (1). This retention or significant residue is due to lower urinary tract dysfunction, in which the cause is usually unknown (idiopathic) or a well-known neurological diseases like spinal cord injury (SCI) or multiple sclerosis (MS). To empty the bladder, the treatment of choice is clean intermittent self-catheterization (CISC) or, clinically less preferred, an indwelling catheter. Patients administer CISC usually 4-6 times a day, keeping the catheterized volume preferably below 400-500 ml (2, 3). In the Netherlands, virtually all patients on CISC utilize single use (=disposable) catheters, which is in contrast to the practice of the use of reusable catheters in several high income non-European countries like Japan, Canada and Australia (4, 5).

Due to exponential population growth, there is an ongoing increase in health-care use, and the consequential rising costs and environmental waste are a widespread concern. The global urinary catheter market size was valued at USD 4.65 billion in 2020, with gradual growth in future perspective. The majority of this market is formed by intermittent single use catheters, which are accountable for around 60% of the market (6). The use of disposable catheters in the Netherlands increased substantially in the past two decades from 15,000 users to 46,000 users, resulting in an expenditure of 74 million euros in 2018 (7). The rising costs and environmental pollution are reasons to reduce the use of disposable catheters. Reusable catheters could be a potential cost and waste reduction opportunity.

Another possible advantages of the reusable catheters include increased patient choice and reducing fear of running out of catheters. Several healthcare insurances, provide up to four catheters a day, which is often not sufficient for the needs of all patients. This introduces potential stress for the patients due to fear of not having enough catheters and does not stimulate the Quality of Life (QoL) of patients. Additionally, it is clear that storage of large amounts of catheters, or travelling for vacation with a stock of catheters, is not ideal for patients.

The current guideline of the European Association of Urology Nurses (EAUN) on intermittent catheterization discusses the possible advantage in favour of the single use catheters based on low (grade 4) level of evidence, mainly concerning the efficacy of cleaning catheters by different methods (8). Other guidelines from the European Urology Association (EAU) and the Dutch society for geriatric specialists (Verenso) do not discuss differences between single use and reusable catheters for CISC (3, 9).

The available literature on the differences in safety and efficacy between single use and reusable catheters is conflicting and of low level of evidence. On the one hand, it has been suggested that reuse of catheters introduces unwanted bacterial contamination and therefore increases the risk of symptomatic urinary tract infections (sUTIs) and other complications, like stone formation and urethral strictures (10). On the other hand, evidence in patients on CISC suggest that reusable catheters are as safe and effective as single use catheters (11). Prieto et al described in their Cochrane analysis of 2014 that there exists no evidence for differences on the incidence of sUTIs in patients using reusable catheters compared to patients using single use catheters (12). This review was forced to withdrawn in 2017 with the argument that more fundamental research was necessary to obtain high level evidence (13). Consulting physicians are willing to prescribe reusable catheters or a mixture of single use and reusable, if the use is substantiated by evidence (14). In view of the lack of this evidence, clinical research is recommended to investigate if the use of reusable catheters is not less safe and not less effective than single use catheters (4, 11). We designed this randomized controlled non-inferiority trial to answer this question.

Methods and Design

Patient and public involvement

This study protocol was designed with the help of patients who administer CISC. The research group was advised in the follow up design, outcome measurements that are important to patients and the practical aspects of the use of the reusable catheter. A member of the Dutch patient advocate group for SCI (DON, Dwarslaesie Organisatie Nederland) was also part of the project-group who wrote the funding application. When implementation of the results of the study will be done, patients will be involved and consulted on the best way to do so, so future adherence will be high.

Trial design and location

This is a multicenter randomized non-inferiority trial, conducted at the urological department of the Erasmus Medical Center (Erasmus MC) in Rotterdam and the following participating Dutch centers: Amphia Hospital in Breda, Franciscus Gasthuis & Vlietland in Rotterdam, Isala Hospital in Zwolle, Treant Care Group in Emmen and Zuyderland Hospital in Heerlen.

Study population

A total of 456 patients will be recruited for this trial. Patients will be included at the outpatient clinic of the urology department of the participating centres. Patients are found eligible if they are ≥ 16 years of age and are diagnosed with urinary retention or significant post-void residue due to non-neurogenic or neurogenic causes. Further in- and exclusion criteria are shown in **table 1**.

Inclusion criteria	**Exclusion criteria**

• Expected chronic, but at least for a duration of twelve months, necessity for daily drainage of the urinary bladder • Be able to administer CISC via the urethra ≥ two times per day and have at least two weeks of experience in CISC	• Temporary use of catheterization because of transient causes • Known significant urethral stricture which prevents CISC • Urinary tract stones • Bladder augmentation • Non-urethral catheterization • History of bladder cancer with active follow-up • The use of immunosuppressives for transplantation or auto-immune diseases • Neurocognitive disease which prevents complete comprehension of the study

Table 1: In- and exclusion criteria.

Recruitment and randomization

Recruitment of participants will be done at the urological departments of the participating study sites. Patients visiting the hospital will be screened for eligibility and asked if they are willing to receive information on the trial. When a patient agrees, further explanation of the study is done by the researchers and the patient information form is send by email or by post. Patients will be given a two week time period to consider participation. When a patient decides to participate, a visit at the hospital will be planned and randomization will be performed after signing the informed consent form. Randomization is done by the tool ALEA (meaning 'dice' in Latin), according to the regulations of the Erasmus MC.

ALEA is developed for randomisation and guarantees concealed allocation. The intervention and control group will be stratified for the participating centres, neurogenic and non-neurogenic causes

for catheterization, age (16-17 years vs. ≥ 18 years and < 50 years vs. ≥ 50 years old), gender, and the female patient group will be balanced for pre- and post-menopausal status.

Study arms

Patients are allocated to one of the two study arms:

Intervention arm

Patients in the intervention arm will start using the Cliny catheter (males) or the PureCath catheter (females). These reusable catheters can be introduced without lubricant because of a high quality smooth surface and will be stored in a holder containing a diluted Milton solution, a cleaning fluid produced by Procter and Gamble which will be renewed every 24 hours. In this trial, the catheter will be used for two weeks. The reusable catheters are CE-marked which indicates that the manufacturer confirms the product's compliance with EU legislation for medical devices (Regulation 2017/745).

Control arm

Patients allocated to the control arm will remain using their own (single use) catheter, the choice of the single use catheter will be determined by the preference of the patient.

Trial objectives and hypothesis

The aim of this trial is to compare single use vs reusable catheters in patients on CISC and to find out if reusing catheters is not less safe and not less efficient as the current single use practice, leading to the following objectives:

Primary Objective:

1. To determine whether reusable catheters are at least not less safe as single use catheters, measured by sUTIs.

Secondary Objectives:

1. To register hospital admissions due to sUTIs or other adverse events due to CISC.

2. To register other adverse events like the number of urethral damage/strictures and kidney/bladder stone formation in both groups.
3. To explore patients' perspective on ease of use and cleaning of the reusable catheters compared to the single use catheters.
4. To determine whether reuse of catheters leads to changes of the urine cultures.
5. To perform economical evaluation of the cost-effectiveness of single use versus reusable catheters.
6. To formulate conclusive recommendations for health care providers and re-formulations of existing protocols.

Our hypothesis is that reusable catheters are as safe and efficient as single use catheters and will provide a significant reduction in healthcare costs and medical waste.

Follow up and study procedures

During the baseline visit, patients are randomized to one of the two study arms and baseline characteristics including a urine specimen for urine culture are collected. After the baseline visit, participants have one week to fill in the first questionnaires before the start of the follow-up (figure 1). The reusable catheters are ordered and delivered at the home of the study participants who are randomized into the intervention arm. After this week, the intervention arm starts with the use of the reusable catheters. One year follow-up will be performed according to the schedule.

Outcome measurements

The main outcome parameters are symptomatic urinary tract infections (sUTIs) and hospital admission due to these sUTIs. The definition of a sUTI used for this trial is based on the criteria of Woodford et al, on the basis of the EAU guidelines on Neurourology and the NHG Guidelines for general practitioners (3, 15, 16).

1. Symptomatic UTI (sUTI): A patient with an acute onset of one or more of the following symptoms: dysuria/pain during catheterization, haematuria, frequency, urgency, urinary retention, suprapubic pain, flank pain, fever, delirium or rigors who did not have a negative urine culture result or a negative nitrite test or a negative dipslide/urine sediment (when taken before receiving antibiotics) or a positive blood culture for a known uropathogen. Additionally, in patients with neurogenic bladder a change in specific symptoms, like increase in incontinence, limb spasm and autonomic dysregulation, could be indicative for a sUTI. The diagnosis is to be decided by the local consultant involved in study.

2. Bacteremic UTI (bUTI): A patient with a blood culture positive for a known uropathogen, providing that their urine culture was not negative (when taken before receiving antibiotics).

Secondary outcome measurements are patient reported outcome measurements (PROMs) on patient satisfaction and QoL, the amount of urethral damage/strictures, kidney- and/or bladder stone formation, episodes of haematuria and possible changes in urinary culture. Furthermore, a cost-effectiveness analysis will be performed in cooperation with the health economist within our project group, using validated questionnaires. Two additional questions concerning patients thoughts on environmental burden and healthcare costs will be asked at baseline and week 52. Other parameters such as patients characteristics, underlying (immune)diseases, hand function and mobility will be assessed as well.

Quality of life and patient satisfaction in study participants

Patient satisfaction and QoL in the intervention arm will be analysed by multiple validated PROMs relative to baseline (before start of the reusable catheter) and the control group. The following PROMs will be used: the five level version of the Euroqol 5D (EQ-5D-5L), for assessing QoL, the Intermittent Self-Catheterization Questionnaire (ISC-Q), which evaluates QoL in CISC patients, the Intermittent Catheterization Satisfaction Questionnaire (InCaSaQ), which evaluates patient satisfaction in CISC patients, and the Patient Global Impression of Improvement (PGI-I). In addition,

the SF-Qualiveen, a short-questionnaire measuring urinary specific QoL is used to evaluate urological symptoms. All PROMs will be completed at baseline, week 6, 26 and 52.

Cost-effectiveness analyses

For the purpose of assessing the cost-effectiveness of reusable catheters data will be collected on medical healthcare utilization, productivity losses and QoL of patients alongside the clinical trial. In this cost-effectiveness study, incremental costs and incremental effects of reusable catheters over single use catheters will be assessed, with effects expressed in quality adjusted life-years (QALYs). The cost-effectiveness study will adhere to the Dutch health economic guidelines. As such the societal perspective will be adopted, meaning that all costs and effects will be included in the analyses, regardless to whom they accrue. The time horizon of the cost-effectiveness study will be equal to the timeframe of the clinical trial. Uncertainty concerning the ICER, QALYs and costs will be assessed using bootstrapping, and this uncertainty will be presented graphically with the CE-acceptability curve. Data on medical healthcare utilization (i.e. volumes) will be collected both through the hospital and by means of the iMTA Medical Consumption Questionnaire (iMCQ). Data on productivity losses will be collected by means of the iMTA Productivity Costs Questionnaire (iPCQ).

Sample size

The number of studies that have investigated the effects of single use and reusable catheters is limited. Nevertheless, recently Prieto et al. (2015) performed an abridged Cochrane review (12). They reported 8 studies that compared single to reusable catheters. For single use 44 events out of 199 were observed, for reusable 44 events out of 191. This leads to the proportions of 0.22 and 0.23. Further we applied a power of 0.80, a one-sided alpha of 0.025 (it is customary to adjust one-sided alphas to the half of 0.05) and a non-inferiority margin of 50% of the mean proportions; 0.11, as is recommended by Althunian et al. (17). The sample size is then calculated with: $n=((Z(1-a)+Z(1-ß))^2 [ps (1-ps)+pe (1-pe)])/((ps-pe-d)^2)$, the formula developed by Blackwelder et al in 1982 (18), leading to

182.4 effective cases in each group. Anticipating a dropout of 20% (19), this must be divided by 80% and rounded upwards. This results in 2 times 228 participants, a total of 456.

Because the lack of comparable non-inferiority designed trials with the same primary outcome measurement (sUTI) it is chosen to look at non-inferiority trials with a primary outcome measurement of (treatment of) sUTI. All these trials handled a non-inferiority marge of 10% (20-24), and two trials even 15% (25, 26). The head researchers and clinicians of the departments of urology and medical microbiology agreed on the 11% marge to be clinical acceptable.

Data collection and management

Data is collected and managed by the researchers in Gemstracker/Limesurvey according to the regulations of the Erasmus MC and the Dutch privacy Law.

Statistical analysis

For analysis of the results, the groups will be stratified for gender and the female patient group will be balanced for pre- and post-menopausal. Data analysis will be performed using SPSS. The primary analysis will be to assess difference between the intervention and the control groups in the sUTI rate and other adverse effects. Descriptive statistics will be used to describe baseline characteristics of participating patients in both groups. Binomial of categorical outcome measures will be analysed using Chi-square tests and quantitative outcome variables by t-tests or Mann-Whitney U tests. Two-sides p values are calculated.

Monitoring

Monitoring will be done according to the requirements of the Netherlands Federation of University Medical Centres (NFU) based on the ICH Good Clinical Practice guidelines. Monitoring will be carried out by qualified monitors of the Clinical Trial Center (CTC) of the Erasmus MC. The frequency of complications due to participation in this trial are expected to be low and of low severity and not more often or severe than in the normal population. Therefore, the investigators classified this study

as a low-risk study. For low-risk clinical trials monitoring will comprise one visit per study site per year.

Discussion

Up to know, no randomized controlled trials with sufficient power have been performed to investigate if the use of reusable catheters for CISC is safe and effective in comparison to single use catheters. Only a small number of studies have been performed after the Cochrane analysis of Prieto et al in 2014 (12, 27-30). These studies did not describe whether a proper cleaning technique was used or if the reused catheter was designed for multiple uses. But most of all, no study obtained an adequate sample size to answer the research question. Therefore, the study described in this protocol will add new insights in the use of reusable catheters and provide high-quality evidence if the sample size is achieved (N=456). However, obtaining the sample size might be a pitfall due to following reason: patients who are randomized into the intervention arm need to use the reusable catheter for a year. The reusable catheter is more time consuming due to the preparation measures for safe use. This could potentially result in higher dropout rate in the intervention arm. To minimize the dropout rate, patients are allowed to use a single use catheter in case of emergency. We therefore drafted the following rule to minimize any non-compliance in the intervention group: a maximum of 20% of the catheterizations per week may be performed with a disposable catheter. All study participants in the intervention group will be frequently asked if and how often they used disposable catheters. We choose for a maximum of 20% so patients who catheterize 6 times a day are a allowed to use one disposable catheter per day, for example during the night.

Only a rough estimation can be made about catheter consumption and the plastic waste generated by this, because it is unclear how many people are dependent on chronic CISC. A recent study explored the use of disposable catheters in the Dutch outpatient setting, revealing a prevalence of almost 46,000 chronic and short-term users in 2018 with an expenditure of 74 million euro (7). Extremely high in comparison to the expenditure of indwelling catheters in the Dutch outpatient

setting (only 6,7 million euro for 54,000 users) (31). Almost 25% of the users had a neurogenic underlying disease, which are usually chronic users with multiple (4-6) catheterizations per day. Based on this assumption, the amount of disposable catheters used on an annual basis for users with a neurogenic underlying disease is more than 20 million disposable catheters a year. If the Dutch neurogenic bladder population only uses reusable catheters, this number could be reduced considerably annually depending on frequency of the duration of usage of the reusable catheter, which is in Japan up to once per 6 weeks and in China up to once per 12 weeks.

If the outcome of this trial leads to a confirmation of non-inferiority of the reusable catheter in comparison to single use catheters, clinical practice will improve and lead to a reduction in health care costs and plastic medical waste in European countries and, ultimately, in the whole world. As a consequence, CISC will also be available in low income countries where the single use catheter at present is much too expensive for the health care system.

Trial status

Currently, the trial is in the recruitment phase.

Declarations

Ethics and dissemination

This study protocol was reviewed and approved by the Medical Ethics Committee of the Erasmus MC (MEC 2019-0134). All participants will sign the informed consent file before entering the trial. This trial will be performed according to the CONSORT checklist for non-inferiority trials. The results of the primary and secondary outcome measurements will be published in an international peer-reviewed journal.

Patient Involvement

Patients, including a patient representative of a relevant patient organization, were involved in the design and conduct of this protocol, including the assessment of the reusable catheter set. During the trial, every patient will be asked to comment on the study design and feasibility of the reusable catheter set.

Author contributions

All authors contributed in the study design. TD and SB drafted this manuscript. JR and BB provided critical revision of the manuscript. TD and BB obtained funding for this trial. All authors approved the final version of the manuscript.

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Competing interests

All authors declare that there are no conflicts of interest.

Figures:

Figure 1. Flowchart of screening and follow-up schedule.

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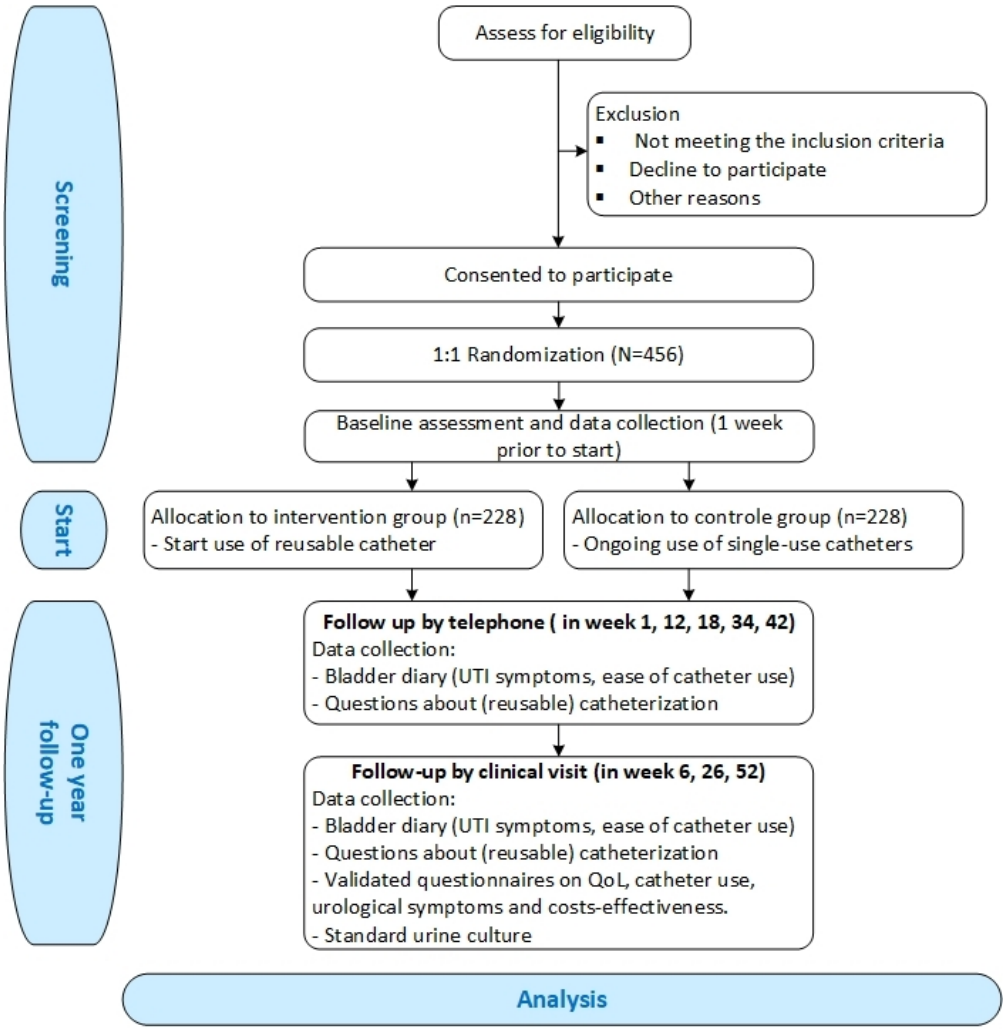

Figure 1. Flowchart of screening and follow-up schedule.

186x190mm (96 x 96 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	X
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6, 11
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9, 10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	X
Sample size	7a	How sample size was determined	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	X
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	x

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	x
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11, 12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Not applicable yet
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Not applicable yet
	14b	Why the trial ended or was stopped	Not applicable yet
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Not applicable yet
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Not applicable yet
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Not applicable yet
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable yet
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable yet
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not applicable yet
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Not applicable yet
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Not applicable yet
Other information			

Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	Not applicable yet
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Single use versus reusable catheters in intermittent CatheterizatiOn for treatment of urinary retention: a protocol for a Multicenter, Prospective, RandomizEd controlled, non-inferiority trial (COMPaRE)

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Single use versus reusable catheters in intermittent CatheterizatiOn for treatment of urinary retention: a protocol for a Multicenter, Prospective, RandomizEd controlled, non-inferiority trial (COMPaRE)

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Abstract

Introduction: Chronic urinary retention is a common lower urinary tract disorder, mostly neurogenic or idiopathic in origin. The preferred treatment is clean intermittent urinary self-catheterization (CISC) four to six times a day. In most European countries, virtually all patients use single use catheters, which is in contrast to several countries where the use of reusable catheters is more common. The available literature on the use of reusable catheters is conflicting and until now, no randomized controlled trial with sufficient power has been performed to investigate if reusable catheters for CISC is as safe as single use catheters.

Methods and analysis: We described this protocol for a prospective, randomized-controlled non-inferiority trial to investigate if the use of reusable catheters is as safe as single use catheters for CISC patients, measured by symptomatic urinary tract infections (sUTIs). Secondary objectives are adverse events due to a sUTI, urethral damage, stone formation, quality of life and patient satisfaction. A cost-effectiveness analysis will also be performed. 456 Participants will be randomized into two groups stratified for age, gender, menopausal status and (non-)neurogenic underlying disorder. The intervention group will replace the reusable catheter set every two weeks for a new set and replace the cleaning solution every 24 hours. The control group continues to use its own catheters. The primary outcome (amount of sUTIs from baseline to one year) will be tested for non-inferiority. Categorical outcome measures will be analysed using Chi-square tests and quantitative outcome variables by t-tests or Mann-Whitney U tests. Two-sides p values will be calculated.

Ethics and dissemination: This protocol was reviewed and approved by the Medical Ethics Committee of the Erasmus MC (MEC 2019-0134) and will be performed according to the SPIRIT checklist for non-inferiority trials. The results of this randomized controlled non-inferiority trial will be published in a peer-reviewed journal and will be publicly available.

Trial registration: Nederlands Trial Register; NL8296 (https://www.trialregister.nl/trial/8296), registered at 14 January 2014.

Article summary

Strengths and limitations of this study:

- This protocol describes a prospective, randomized-controlled, non-inferiority study and will provide information regarding the safety, effectiveness, patient satisfaction and costs-effectiveness of reusable catheters in comparison to single use catheters in patients on CISC of the urinary bladder.
- It is the first study protocol with a sufficient sample size calculation able to detect non-inferiority for the reusable catheter measured by sUTIs.
- The definition of a sUTI is fully and clearly defined in this protocol.
- The steps involved in using the reusable catheter set are more time consuming. This might result in a higher dropout rate in the intervention arm.
- Non-inferiority of the reusable catheter for sUTIs has the following implications: increased patients choice and reducing fear of running out of catheters, a reduction in health care costs and plastic medical waste and the opportunity for patients in low income countries to perform CISC with a reusable catheter as the single use catheter at present is much too expensive for the health care systems in low income countries.

Keywords: clean intermittent catheterization, urinary retention, underactive bladder, single use catheters, reusable catheters, randomized controlled trial, non-inferiority trial

Background

Millions of people have difficulty in emptying their urinary bladder resulting in urinary retention or clinically significant post void residue (PVR) (1). Urinary retention or significant urinary residue is due to lower urinary tract dysfunction, which can be caused by well-known neurological diseases like spinal cord injury (SCI) or multiple sclerosis (MS), or in some cases it can be idiopathic. To empty the bladder, the treatment of choice is clean intermittent self-catheterization (CISC) or, clinically less preferred, an indwelling catheter. Patients administer CISC usually 4-6 times a day, keeping the catheterized volume preferably below 400-500 ml (2, 3). In the Netherlands, virtually all patients on CISC utilize single use (=disposable) catheters, which is in contrast to several high income non-European countries like Japan, Canada and Australia (4, 5). In those countries, single use and reusable catheters are both used for CISC.

Due to exponential population growth, there is an ongoing increase in health-care use, and the consequential rising costs and environmental waste are a widespread concern. The global urinary catheter market size was valued at USD 4.65 billion in 2020, with gradual growth in future perspective. The majority of this market is formed by intermittent single use catheters, which are accountable for around 60% of the market (6). The use of disposable catheters in the Netherlands increased substantially in the past two decades from 15,000 users to 46,000 users, resulting in an expenditure of 74 million euros in 2018 (7). The rising costs and environmental pollution are reasons to reduce the use of disposable catheters. Reusable catheters could be a potential cost and waste reduction opportunity.

Another possible advantages of the reusable catheters include increased patient choice and reducing fear of running out of catheters. Several healthcare insurances, provide up to four catheters a day, which is often not sufficient for the needs of all patients. This potentially introduces stress for the patients due to fear of not having enough catheters and does not stimulate the Quality of Life (QoL)

of patients. Additionally, it is clear that storage of large amounts of catheters, or travelling with a stock of catheters, is not ideal for patients.

The current guideline of the European Association of Urology Nurses (EAUN) on intermittent catheterization discusses the possible advantage in favour of the single use catheters based on low (grade 4) level of evidence, mainly concerning the efficacy of cleaning catheters by different methods (8). Other guidelines from the European Urology Association (EAU) and the Dutch society for geriatric specialists (Verenso) do not discuss differences between single use and reusable catheters for CISC (3, 9).

The available literature on the differences in safety and efficacy between single use and reusable catheters is conflicting and of low level of evidence. On the one hand, it has been suggested that reuse of catheters introduces unwanted bacterial contamination and therefore increases the risk of symptomatic urinary tract infections (sUTIs) and other complications, like stone formation and urethral strictures (10). On the other hand, evidence in patients on CISC suggest that reusable catheters are as safe and effective as single use catheters (11). Prieto et al reported in their Cochrane analysis of 2021 that they are uncertain whether there is any difference between single use and multiple-use catheters in the risk of sUTIs because the certainty of the evidence is low. (12, 13). Consultant physicians are willing to prescribe reusable catheters or a mixture of single use and reusable, if the use is substantiated by evidence (14). In view of the lack of this evidence, clinical research is recommended to investigate if the use of reusable catheters are not less safe than single use catheters (4, 11). We designed this randomized controlled non-inferiority trial to answer this question.

Methods and Design

Patient and public involvement

This study protocol was designed with the help of patients who administer CISC. Several chronic CISC patients have assessed the reusable catheter set by examining and holding it in detail. The research group was advised in the follow-up design, outcome measurements that are important to patients and the practical aspects of the use of this specially designed reusable catheter set. A member of the Dutch patient advocate group for SCI (DON, Dwarslaesie Organisatie Nederland) was also part of the project-group who wrote the funding application. Patients will be involved and consulted on the best way to implement the results of this study in order to guarantee that future adherence will be high.

Trial design and location

This is a multicenter randomized non-inferiority trial, conducted at the urological department of the Erasmus Medical Center (Erasmus MC) in Rotterdam and the following participating Dutch centers: Amphia Hospital in Breda, Franciscus Gasthuis & Vlietland in Rotterdam, Isala Hospital in Zwolle, Treant Care Group in Emmen and Zuyderland Hospital in Heerlen.

Study population

A total of 456 patients will be recruited for this trial. Patients will be included at the outpatient clinic of the urology department of the participating centres. Patients are found eligible if they are ≥ 16 years of age and are diagnosed with urinary retention or significant post-void residue due to non-neurogenic or neurogenic causes. Further in- and exclusion criteria are shown in **table 1**.

Inclusion criteria	**Exclusion criteria**

• Expected chronic, but at least for a duration of twelve months, necessity for daily drainage of the urinary bladder • Be able to administer CISC via the urethra ≥ two times per day and have at least two weeks of experience in CISC	• Temporary use of catheterization because of transient causes • Known significant urethral stricture which prevents CISC • Urinary tract stones • Bladder augmentation • Non-urethral catheterization • History of bladder cancer with active follow-up • The use of immunosuppressives for transplantation or auto-immune diseases • Neurocognitive disease which prevents complete comprehension of the study

Table 1: In- and exclusion criteria.

Recruitment

Participants will be recruited at the urological departments of the participating study sites. Patients visiting the hospital will be screened for eligibility and asked if they are willing to receive information on the trial. Patients who are interested to participate will be informed about the study design and the use of the Cliny and PureCath products. First, patients receive an explanation by telephone about the study design and the reusable catheter. If patients are still interested, a comprehensive patient information folder and an instruction video of the reusable catheter will be sent by email to all eligible patients. Patients will be given a minimum of one week to consider participation. When a patient decides to participate, a clinical visit is scheduled to demonstrate the reusable catheters. During this visit, the catheters will be demonstrated and it will be checked if the patient has understood all information. If the researcher (M.D. or research nurse) is convinced that the patient understands what participation entails, they will proceed to signing the informed consent form (see online supplementary file 1).

Randomization

Randomization is done by the tool ALEA (meaning 'dice' in Latin), according to the regulations of the Erasmus MC. ALEA is developed for randomisation and guarantees concealed allocation. The intervention and control group will be stratified for the participating centres, neurogenic and non-neurogenic causes for catheterization, age (16-17 years vs. ≥ 18 years and < 50 years vs. ≥ 50 years old), gender, and the female patient group will be balanced for pre- and post-menopausal status. Upon randomization, patients will be allocated a unique study subject number in chronologically ascending order for every study site, starting with 1 (for example Erasmus MC : EMC001). They will be randomized to the intervention arm (reusable catheter) or control arm (single use catheter). There is no pre-specified list upon randomization, but each combination of stratification factors will form a combination. Within each combination, ALEA will randomly assign a study arm. The rational for this approach is that it will maximize the probability of assigning a new participant in the study arm with the lowest number of patients. The company for the randomization procedure is the Clinical Trial Center of the Erasmus MC.

Blinding

Blinding of the study participants and clinical research staff is impossible due to the different appearances and conditions of the disposable catheters and reusable catheters for CISC. The statistician involved, will be blinded for the intervention and control group during the analysis.

Study arms

Patients are allocated to one of the two study arms:

Intervention arm

Patients in the intervention arm will start using the Cliny catheter (males) or the PureCath catheter (females). These reusable catheters can be introduced without lubricant because of a high quality smooth surface and will be stored in a holder containing a diluted 2% sodium hypochlorite solution, which will be renewed every 24 hours. The 2% sodium hypochlorite solution is diluted with cold tap water (1:80). In this trial, the catheter will be used for two weeks. The reusable catheters are CE-

marked which indicates that the manufacturer confirms the product's compliance with EU legislation for medical devices (Regulation 2017/745). The manufacturer of the reusable catheter tested the compatibility of cleaning solution with the reusable catheters and recommended the use of 0.6% dilution of 2% sodium hypochlorite w/w solution as cleaning method.

Control arm

Patients allocated to the control arm will remain using their own (single use) catheter, the choice of the single use catheter will be determined by the preference of the patient.

If a study participant no longer requires or is no longer able to safely self-catheterize, the study participation will be terminated and registered as a dropout.

Trial objectives and hypothesis

The primary aim of this trial is to compare single use vs reusable catheters in patients on CISC and to find out if reusing catheters is as safe as the current single use practice, leading to the following primary objective: to determine whether reusable catheters are as safe as single use catheters, measured by sUTIs.

Our secondary objectives are to investigate the safety, efficiency and costs-effectiveness of the reusable catheter and to explore patient opinions on the reusable catheter. Table 2 provides an overview of all objectives and outcome measures.

Objectives	Primary outcome	Secondary outcome	Measured by
Safety To determine whether reusable catheters are at least not less safe as single use catheters	Amount of sUTI	 - Hospitalization due to a sUTI - Bacteremic UTI - Urethral damage leading to clinical significant strictures - Kidney/bladder stone formation - Episodes of macroscopic hematuria	- sUTI (see definition) - sUTI + hospitalization records - sUTI + positive blood culture - Anamnestic - Anamnestic - Anamnestic
Efficiency To investigate whether reusable catheters are not less efficient as single use catheters	X	- Patient satisfaction - Quality of Life (QoL)	- PROMs: ISCQ, InCaSaQ, PGI-I - PROM: EQ-5D-5L
Costs-effectiveness To investigate whether reusable catheters are costs-effective in comparison to single use catheters	X	- Quality-adjusted-life-years (QALYs) and incremental costs-effecitiveness ratios (ICER)	- Hospital records - PROMs: iMCQ, iPCQ, EQ-5D-5L

Patient opinions To explore patients opinions on health care costs and environmental burden in the context of CISC	X	- Patient opinion	- Two statement questions answered by a Likert-scale from 1 – 5 (fully agree – fully disagree)

Table 2. Overview of all objectives and outcome measures.

Our hypothesis is that reusable catheters are as safe and efficient as single use catheters and will provide a significant reduction in healthcare costs and medical waste.

Follow up and study procedures

During the baseline visit, patients are randomized to one of the two study arms and baseline characteristics including a urine specimen for urine culture are collected. After the baseline visit, participants have one week to fill in the first questionnaires before the start of the follow-up period (figure 1). The reusable catheters are ordered and delivered at the home of the study participants who are randomized into the intervention arm. After this week, the intervention arm starts with the use of the reusable catheters. One year follow-up will be performed according to the schedule.

Primary outcome measure

The main outcome parameters are symptomatic urinary tract infections (sUTIs). The definition of a sUTI used for this trial is based on the criteria of Woodford et al, on the basis of the EAU guidelines on Neurourology and the NHG Guidelines for Dutch general practitioners (3, 15, 16).

Symptomatic UTI (sUTI): A patient must meet 1 and 2 below:

1. An acute onset of one or more of the following symptoms:

   - dysuria / pain during catheterization
   - Haematuria
   - Urinary frequency
   - Urinary urgency
   - Suprapubic pain
   - Flank pain

- Fever (> 38 ° C)
- Rigors
- Delirium
- In case of a neurogenic bladder: a change in specific symptoms, like increased urinary incontinence, limb spasm and autonomic dysregulation, could be indicative for a sUTI.

2. and one of the following positive diagnostic tests
   - positive urine culture
   - Positive dipslide
   - Positive nitrite test
   - Positive urine sediment

The diagnosis is to be decided by the local consultant involved in study.

Secondary outcome measures

An overview of all outcome measures is provided in table 2. Other parameters such as patients characteristics, possible changes in urine cultures over time, underlying (immune)diseases, hand function and mobility will be assessed as well.

Secondary safety outcome measures

The following secondary outcome measures are used to investigate the safety of the reusable catheters: the amount of bacteremic UTI (bUTI), hospitalizations due to sUTI, urethral damage leading to clinical significant strictures, clinical significant kidney- and/or bladder stone formation and episodes of macroscopic hematuria.

Bacteremic UTI (bUTI) is defined as a patient with a sUTI and a blood culture positive for a known uropathogen, providing that their urine culture matches the positive blood culture (in case a urine culture was taken before receiving antibiotics).

Quality of life and patient satisfaction in study participants

Patient satisfaction and QoL in the intervention arm will be analysed by multiple validated patient reported outcome measurements (PROMs) relative to baseline (before start of the reusable catheter) and the control group. The following PROMs will be used: the five level version of the Euroqol 5D (EQ-5D-5L), for assessing QoL (17), the Intermittent Self-Catheterization Questionnaire (ISC-Q), which evaluates QoL in CISC patients, the Intermittent Catheterization Satisfaction Questionnaire (InCaSaQ), which evaluates patient satisfaction in CISC patients(18), and the Patient Global Impression of Improvement (PGI-I) (19). In addition, the SF-Qualiveen, a short-questionnaire measuring urinary specific QoL is used to evaluate urological symptoms (20). All PROMs will be completed at baseline, week 6, 26 and 52.

Patients opinions

Two additional questions concerning patients thoughts on environmental burden and healthcare costs will be asked at baseline and week 52.

Cost-effectiveness analysis

For the purpose of assessing the cost-effectiveness of reusable catheters data will be collected on medical healthcare utilization, productivity losses and QoL of patients alongside the clinical trial. In this cost-effectiveness study, incremental costs and incremental effects of reusable catheters over single use catheters will be assessed, with effects expressed in quality adjusted life-years (QALYs). The cost-effectiveness study will adhere to the Dutch health economic guidelines (21) and will be performed by the institute for Medical Technology Assessment (iMTA) of the Erasmus University in Rotterdam (EUR). As such the societal perspective will be adopted, meaning that all costs and effects will be included in the analysis, regardless to whom they accrue. The time horizon of the cost-effectiveness study will be equal to the timeframe of the clinical trial. Uncertainty concerning the incremental cost-effectiveness ratios (ICER), QALYs and costs will be assessed using bootstrapping, and this uncertainty will be presented graphically with the CE-acceptability curve. Data on medical

healthcare utilization (i.e. volumes) will be collected both through hospital records and by means of the iMTA Medical Consumption Questionnaire (iMCQ) (22). Data on productivity losses will be collected by means of the iMTA Productivity Costs Questionnaire (iPCQ) (23). We will use a willingness to pay (WTP) threshold of €20,000/QALY, based on the reference value for cost-effectiveness determined by the National Health Care Institute of The Netherlands (21). A study on health-economic burden of urinary-catheter-associated infection in England used a similar WTP threshold of £20,000/QALY based on the NICE guidelines (24, 25).

Sample size

The number of studies that have investigated the effects of single use and reusable catheters is limited. Nevertheless, recently Prieto et al. (2015) performed an abridged Cochrane review (26). They reported 8 studies that compared single to reusable catheters. For single use 44 events out of 199 were observed, for reusable 44 events out of 191. This leads to the proportions of 0.22 and 0.23. Further we applied a power of 0.80, a one-sided alpha of 0.025 (it is customary to adjust one-sided alphas to the half of 0.05) and a non-inferiority margin of 50% of the mean proportions; 0.11, as is recommended by Althunian et al. (27). The sample size is then calculated with: $n=((Z(1-a)+Z(1-ß))^2$ [ps (1-ps)+pe (1-pe)])/((ps-pe-d)^2), the formula developed by Blackwelder et al in 1982 (28), leading to 182.4 effective cases in each group. Anticipating a dropout of 20% (29), this must be divided by 80% and rounded upwards. This results in 2 times 228 participants, a total of 456.

Because the lack of comparable non-inferiority designed trials on reusable catheters for CISC with the same primary outcome measurement (sUTI), we chose to look at other non-inferiority trials with a primary outcome measurement of sUTI in patients on CISC. All these trials handled a non-inferiority marge of 10% (30-34), and two trials even 15% (35, 36). The head researchers and clinicians of the departments of urology and medical microbiology agreed on the 11% marge to be clinical acceptable.

Data collection and management

Data is collected and managed by the (site) researchers in Gemstracker/Limesurvey according to the regulations of the Erasmus MC and the Dutch privacy Law. (Site) investigators will supervise the day-to-day operation of the project and are responsible for ensuring that the Good Clinical Practice guidelines are followed.

Statistical analysis

For analysis of the results, the groups will be stratified for gender and the female patient group will be balanced for pre- and post-menopausal. Data analysis will be performed using SPSS. The primary analysis will be to assess difference between the intervention and the control groups in the sUTI rate using a risk difference and 95% to determine non-superiority. Descriptive statistics will be used to describe baseline characteristics of participating patients in both groups. Binomial of categorical outcome measures will be analysed using Chi-square tests and quantitative outcome variables by t-tests or Mann-Whitney U tests. Two-sides p values are calculated.

Monitoring

Monitoring will be done according to the requirements of the Netherlands Federation of University Medical Centres (NFU) based on the ICH Good Clinical Practice guidelines. Monitoring will be carried out by qualified monitors of the Clinical Trial Center (CTC) of the Erasmus MC. The frequency of complications due to participation in this trial are expected to be low and of low severity and not more often or severe than in the general population. Therefore, the Medical Ethical committee of the Erasmus MC classified this study as a low-risk study. For low-risk clinical trials monitoring will comprise one visit per study site per year.

All adverse events will be registered and classified according to the Common Terminology Criteria for Adverse Events published by the National Institutes of Health of the United States of America (37). In case of a serious adverse event (grade 3 or more), this will be reported to the testing authorities (ToetsingOnline). ToetsingOnline are in control to decide if an early interim analysis is needed to ensure the safety of this trial.

Discussion

Up to now, no randomized controlled trials with sufficient power have been performed to investigate if the use of reusable catheters for CISC is safe and effective in comparison to single use catheters. Only a small number of studies have been performed after the Cochrane analysis of Prieto et al in 2014 (26, 38-41). These studies did not describe whether a proper cleaning technique was used or if the reused catheter was designed for multiple uses. But most of all, no study obtained an adequate sample size to answer the research question. Therefore, the study described in this protocol will add new insights in the use of reusable catheters and provide high-quality evidence if the sample size is achieved (N=456). However, obtaining the sample size might be a pitfall due to following reason: patients who are randomized into the intervention arm need to use the reusable catheter for a year. The reusable catheter is more time consuming due to the preparation measures for safe use. This could potentially result in higher dropout rate in the intervention arm. To minimize the dropout rate, patients are allowed to use a single use catheter in case of emergency. We therefore drafted the following rule to minimize any non-compliance in the intervention group: a maximum of 20% of the catheterizations per week may be performed with a disposable catheter. All study participants in the intervention group will be frequently asked if and how often they used disposable catheters. We chose a maximum of 20% so patients who catheterize 6 times a day are a allowed to use one disposable catheter per day, for example during the night.

Only a rough estimation can be made about catheter consumption and the plastic waste generated by this, because it is unclear how many people are dependent on chronic CISC. A recent study explored the use of disposable catheters in the Dutch outpatient setting, revealing a prevalence of almost 46,000 chronic and short-term users in 2018 with an expenditure of 74 million euro (7). Extremely high in comparison to the expenditure of indwelling catheters in the Dutch outpatient setting (only 6,7 million euro for 54,000 users) (42). Almost 25% of the users had a neurogenic underlying disease, which are usually chronic users with multiple (4-6) catheterizations per day.

Based on this assumption, the amount of disposable catheters used on an annual basis for users with a neurogenic underlying disease is more than 20 million disposable catheters a year. If the Dutch neurogenic bladder population only uses reusable catheters, this number could be reduced considerably annually depending on frequency of replacement of the reusable catheter, which is in Japan once per 6 weeks and in China once per 12 weeks.

If the outcome of this trial leads to a confirmation of non-inferiority of the reusable catheter in comparison to single use catheters, clinical practice will improve and lead to a reduction in health care costs and plastic medical waste in European countries and, ultimately, in the whole world. As a consequence, CISC will also be available in low income countries where the single use catheter at present is much too expensive for the health care system.

Trial status

Currently, the trial is in the recruitment phase.

Declarations

Ethics and dissemination

This study protocol (issue date: 20 September 2019, version 3.0) was reviewed and approved by the Medical Ethics Committee of the Erasmus MC (MEC 2019-0134). All participants will sign the informed consent form before entering the trial. This trial will be performed according to the SPIRIT checklist for non-inferiority trials (see online supplementary file 2). The results of the primary and secondary outcome measurements will be published in an international peer-reviewed journal.

Patient Involvement

Patients, including a patient representative of a relevant patient organization, were involved in the design and conduct of this protocol, including the assessment of the reusable catheter set. During the trial, every patient will be asked to comment on the study and the design of the reusable catheter set.

Author contributions

All authors contributed in the study design. TD and SB drafted this manuscript. JR and BB provided critical revision of the manuscript. TD and BB obtained funding for this trial. All authors approved the final version of the manuscript.

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Competing interests

All authors declare that there are no conflicts of interest.

Data sharing statement

The final trial dataset will be available to study investigators, Steering Committee members and the Research ethic Board at all participating centers.

Compensation of Research Participants

Study participants are reimbursed for the travel costs of four clinical study visits. Each visit is compensated with 20 euros.

Figures:

*Figure 1. Flowchart of screening and follow-up schedule. *UTI symptoms: urinary tract symptoms, QoL: quality of life.*

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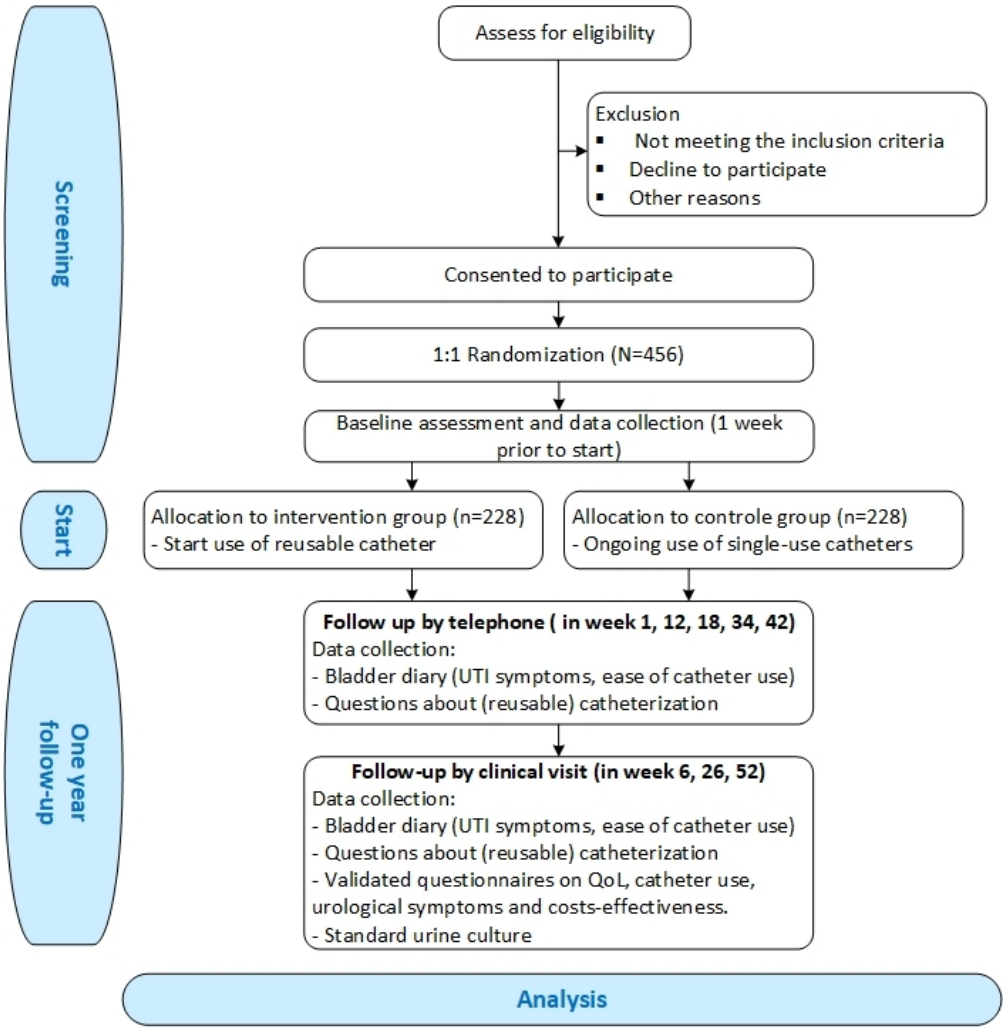

Figure 1. Flowchart of screening and follow-up schedule.

186x190mm (96 x 96 DPI)

Appendix C: Subject informed consent form

"The reuse of catheters in patients who catheterize intermittently"

- I have read the information sheet. I was able to ask questions. My questions have been answered well enough. I had enough time to decide if I want to participate.
- I know that taking part is voluntary. I also know that I can decide at any time not to participate or to stop the study. I do not have to explain why.
- I give consent to inform the general practitioner/specialist(s) who treats me that I am participating in this study and that I will potentially use a reusable catheter.
- I give consent to request information from my general practitioner/specialist(s) about the results from urine analysis and side effects.
- I give consent to request information from the laboratory where the urine analyses were performed.
- I give consent to collect and use my data and body material to answer the research question of this study.
- I know that for the monitoring of this research some people can get access to all my data. These people are listed in this information sheet. I give consent for access by these people.

- I give consent to keep my personal information for a period of 15 years and to use it for future research in the field of my condition and/or the investigated treatment method.

  □ **Yes**

  □ **No**

- I give consent to have my body material stored after this study for use in other research, as stated in the information sheet.

  □ **Yes**

  □ **No**

- I give consent to ask me after this study if I want to participate in a follow-up study.

  □ **Yes**

  □ **No**

- I want to participate in this study.

Name of the subject:

Signature: Date : __ / __ / __

I declare that I have fully informed this subject about the above study.

If any information becomes known during the study that could influence the subject's consent, I will let them know in good time.

Investigator name (or their representative):
Signature: Date: __ / __ / __

Additional information was given by:
Name:
Job title:
Signature: Date: __ / __ / __

---

* Delete what is not applicable.

The subject will receive a complete information sheet, together with a signed version of the consent form.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1 +2 + 17
Protocol version	3	Date and version identifier	17
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13 + 14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4 + 5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6+7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8 +9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	x
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	x
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10, 11, table 2_
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1.

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	X

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10 - 13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	x

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	x
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	x
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Supl 1
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supl 1
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	18
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	x
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Suppl 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	x

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Single use versus reusable catheters in intermittent CatheterizatiOn for treatment of urinary retention: a protocol for a Multicenter, Prospective, RandomizEd controlled, non-inferiority trial (COMPaRE)

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Keywords:	UROLOGY, Clinical trials < THERAPEUTICS, Bladder disorders < UROLOGY, Adult urology < UROLOGY, Neuro-urology < UROLOGY, Paediatric urology < UROLOGY

Single use versus reusable catheters in intermittent CatheterizatiOn for treatment of urinary retention: a protocol for a Multicenter, Prospective, RandomizEd controlled, non-inferiority trial (COMPaRE)

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Abstract

Introduction: Chronic urinary retention is a common lower urinary tract disorder, mostly neurogenic or idiopathic in origin. The preferred treatment is clean intermittent urinary self-catheterization (CISC) four to six times a day. In most European countries, virtually all patients use single use catheters, which is in contrast to several countries where the use of reusable catheters is more common. The available literature on the use of reusable catheters is conflicting and until now, no randomized controlled trial with sufficient power has been performed to investigate if reusable catheters for CISC is as safe as single use catheters.

Methods and analysis: We described this protocol for a prospective, randomized-controlled non-inferiority trial to investigate if the use of reusable catheters is as safe as single use catheters for CISC patients, measured by symptomatic urinary tract infections (sUTIs). Secondary objectives are adverse events due to a sUTI, urethral damage, stone formation, quality of life and patient satisfaction. A cost-effectiveness analysis will also be performed. 456 Participants will be randomized into two groups stratified for age, gender, menopausal status and (non-)neurogenic underlying disorder. The intervention group will replace the reusable catheter set every two weeks for a new set and replace the cleaning solution every 24 hours. The control group continues to use its own catheters. The primary outcome (amount of sUTIs from baseline to one year) will be tested for non-inferiority. Categorical outcome measures will be analysed using Chi-square tests and quantitative outcome variables by t-tests or Mann-Whitney U tests. Two-sides p values will be calculated.

Ethics and dissemination: This protocol was reviewed and approved by the Medical Ethics Committee of the Erasmus MC (MEC 2019-0134) and will be performed according to the SPIRIT checklist for non-inferiority trials. The results of this randomized controlled non-inferiority trial will be published in a peer-reviewed journal and will be publicly available.

Trial registration: Nederlands Trial Register; NL8296 (https://www.trialregister.nl/trial/8296), registered at 14 January 2020.

Article summary

Strengths and limitations of this study:

- This protocol describes a prospective, randomized-controlled, non-inferiority study and will provide information regarding the safety, effectiveness, patient satisfaction and costs-effectiveness of reusable catheters in comparison to single use catheters in patients on CISC of the urinary bladder.
- It is the first study protocol with a sufficient sample size calculation able to detect non-inferiority for the reusable catheter measured by sUTIs.
- The definition of a sUTI is fully and clearly defined in this protocol.
- The steps involved in using the reusable catheter set are more time consuming. This might result in a higher dropout rate in the intervention arm.
- Non-inferiority of the reusable catheter for sUTIs has the following implications: increased patients choice and reducing fear of running out of catheters, a reduction in health care costs and plastic medical waste and the opportunity for patients in low income countries to perform CISC with a reusable catheter as the single use catheter at present is much too expensive for the health care systems in low income countries.

Keywords: clean intermittent catheterization, urinary retention, underactive bladder, single use catheters, reusable catheters, randomized controlled trial, non-inferiority trial

Background

Millions of people have difficulty in emptying their urinary bladder resulting in urinary retention or clinically significant post void residue (PVR) (1). Urinary retention or significant urinary residue is due to lower urinary tract dysfunction, which can be caused by well-known neurological diseases like spinal cord injury (SCI) or multiple sclerosis (MS), or in some cases it can be idiopathic. To empty the bladder, the treatment of choice is clean intermittent self-catheterization (CISC) or, clinically less preferred, an indwelling catheter. Patients administer CISC usually 4-6 times a day, keeping the catheterized volume preferably below 400-500 ml (2, 3). In the Netherlands, virtually all patients on CISC utilize single use (=disposable) catheters, which is in contrast to several high income non-European countries like Japan, Canada and Australia (4, 5). In those countries, single use and reusable catheters are both used for CISC.

Due to exponential population growth, there is an ongoing increase in health-care use, and the consequential rising costs and environmental waste are a widespread concern. The global urinary catheter market size was valued at USD 4.65 billion in 2020, with gradual growth in future perspective. The majority of this market is formed by intermittent single use catheters, which are accountable for around 60% of the market (6). The use of disposable catheters in the Netherlands increased substantially in the past two decades from 15,000 users to 46,000 users, resulting in an expenditure of 74 million euros in 2018 (7). The rising costs and environmental pollution are reasons to reduce the use of disposable catheters. Reusable catheters could be a potential cost and waste reduction opportunity.

Another possible advantages of the reusable catheters include increased patient choice and reducing fear of running out of catheters. Several healthcare insurances, provide up to four catheters a day, which is often not sufficient for the needs of all patients. This potentially introduces stress for the patients due to fear of not having enough catheters and does not stimulate the Quality of Life (QoL)

of patients. Additionally, it is clear that storage of large amounts of catheters, or travelling with a stock of catheters, is not ideal for patients.

The current guideline of the European Association of Urology Nurses (EAUN) on intermittent catheterization discusses the possible advantage in favour of the single use catheters based on low (grade 4) level of evidence, mainly concerning the efficacy of cleaning catheters by different methods (8). Other guidelines from the European Urology Association (EAU) and the Dutch society for geriatric specialists (Verenso) do not discuss differences between single use and reusable catheters for CISC (3, 9).

The available literature on the differences in safety and efficacy between single use and reusable catheters is conflicting and of low level of evidence. On the one hand, it has been suggested that reuse of catheters introduces unwanted bacterial contamination and therefore increases the risk of symptomatic urinary tract infections (sUTIs) and other complications, like stone formation and urethral strictures (10). On the other hand, evidence in patients on CISC suggest that reusable catheters are as safe and effective as single use catheters (11). Prieto et al reported in their Cochrane analysis of 2021 that they are uncertain whether there is any difference between single use and multiple-use catheters in the risk of sUTIs because the certainty of the evidence is low. (12, 13). Consultant physicians are willing to prescribe reusable catheters or a mixture of single use and reusable, if the use is substantiated by evidence (14). In view of the lack of this evidence, clinical research is recommended to investigate if the use of reusable catheters are not less safe than single use catheters (4, 11). We designed this randomized controlled non-inferiority trial to answer this question.

Methods and Design

Patient and public involvement

This study protocol was designed with the help of patients who administer CISC. Several chronic CISC patients have assessed the reusable catheter set by examining and holding it in detail. The research group was advised in the follow-up design, outcome measurements that are important to patients and the practical aspects of the use of this specially designed reusable catheter set. A member of the Dutch patient advocate group for SCI (DON, Dwarslaesie Organisatie Nederland) was also part of the project-group who wrote the funding application. Patients will be involved and consulted on the best way to implement the results of this study in order to guarantee that future adherence will be high.

Trial design and location

This is a multicenter randomized non-inferiority trial, conducted at the urological department of the Erasmus Medical Center (Erasmus MC) in Rotterdam and the following participating Dutch centers: Amphia Hospital in Breda, Franciscus Gasthuis & Vlietland in Rotterdam, Isala Hospital in Zwolle, Treant Care Group in Emmen and Zuyderland Hospital in Heerlen.

Study population

A total of 456 patients will be recruited for this trial. Patients will be included at the outpatient clinic of the urology department of the participating centres. Patients are found eligible if they are ≥ 16 years of age and are diagnosed with urinary retention or significant post-void residue due to non-neurogenic or neurogenic causes. Further in- and exclusion criteria are shown in **table 1**.

Inclusion criteria	**Exclusion criteria**

• Expected chronic, but at least for a duration of twelve months, necessity for daily drainage of the urinary bladder • Be able to administer CISC via the urethra ≥ two times per day and have at least two weeks of experience in CISC	• Temporary use of catheterization because of transient causes • Known significant urethral stricture which prevents CISC • Urinary tract stones • Bladder augmentation • Non-urethral catheterization • History of bladder cancer with active follow-up • The use of immunosuppressives for transplantation or auto-immune diseases • Neurocognitive disease which prevents complete comprehension of the study

Table 1: In- and exclusion criteria.

Recruitment

Participants will be recruited at the urological departments of the participating study sites. Patients visiting the hospital will be screened for eligibility and asked if they are willing to receive information on the trial. Patients who are interested to participate will be informed about the study design and the use of the Cliny and PureCath products. First, patients receive an explanation by telephone about the study design and the reusable catheter. If patients are still interested, a comprehensive patient information folder and an instruction video of the reusable catheter will be sent by email to all eligible patients. Patients will be given a minimum of one week to consider participation. When a patient decides to participate, a clinical visit is scheduled to demonstrate the reusable catheters. During this visit, the catheters will be demonstrated and it will be checked if the patient has understood all information. If the researcher (M.D. or research nurse) is convinced that the patient understands what participation entails, they will proceed to signing the informed consent form (see online supplementary file 1).

Randomization

Randomization is done by the tool ALEA (meaning 'dice' in Latin), according to the regulations of the Erasmus MC. ALEA is developed for randomisation and guarantees concealed allocation. The intervention and control group will be stratified for the participating centres, neurogenic and non-neurogenic causes for catheterization, age (16-17 years vs. ≥ 18 years and < 50 years vs. ≥ 50 years old), gender, and the female patient group will be balanced for pre- and post-menopausal status. Upon randomization, patients will be allocated a unique study subject number in chronologically ascending order for every study site, starting with 1 (for example Erasmus MC : EMC001). They will be randomized to the intervention arm (reusable catheter) or control arm (single use catheter). There is no pre-specified list upon randomization, but each combination of stratification factors will form a combination. Within each combination, ALEA will randomly assign a study arm. The rational for this approach is that it will maximize the probability of assigning a new participant in the study arm with the lowest number of patients. The company for the randomization procedure is the Clinical Trial Center of the Erasmus MC.

Blinding

Blinding of the study participants and clinical research staff is impossible due to the different appearances and conditions of the disposable catheters and reusable catheters for CISC. The statistician involved, will be blinded for the intervention and control group during the analysis.

Study arms

Patients are allocated to one of the two study arms:

Intervention arm

Patients in the intervention arm will start using the Cliny catheter (males) or the PureCath catheter (females). These reusable catheters can be introduced without lubricant because of a high quality smooth surface and will be stored in a holder containing a diluted 2% sodium hypochlorite solution, which will be renewed every 24 hours. The 2% sodium hypochlorite solution is diluted with cold tap water (1:80). In this trial, Milton fluid (a product of Procter and Gamble) is used to clean and store

the catheter. To reduce the risk of damage from the cleaning solution, the catheter is rinsed with cold tap water prior to each use. Every reusable catheter will be used for two weeks. The reusable catheters are CE-marked which indicates that the manufacturer confirms the product's compliance with EU legislation for medical devices (Regulation 2017/745). The manufacturer of the reusable catheter tested the compatibility of cleaning solution with the reusable catheters and recommended the use of 0.6% dilution of 2% sodium hypochlorite w/w solution as cleaning method.

Control arm

Patients allocated to the control arm will remain using their own (single use) catheter, the choice of the single use catheter will be determined by the preference of the patient.

If a study participant no longer requires or is no longer able to safely self-catheterize, the study participation will be terminated and registered as a dropout.

Trial objectives and hypothesis

The primary aim of this trial is to compare single use vs reusable catheters in patients on CISC and to find out if reusing catheters is as safe as the current single use practice, leading to the following primary objective: to determine whether reusable catheters are as safe as single use catheters, measured by sUTIs.

Our secondary objectives are to investigate the safety, efficiency and costs-effectiveness of the reusable catheter and to explore patient opinions on the reusable catheter. Table 2 provides an overview of all objectives and outcome measures.

Objectives	Primary outcome	Secondary outcome	Measured by
Safety To determine whether reusable catheters are at least not less safe as single use catheters	Number of sUTIs	 - Hospitalization due to a sUTI - Bacteremic UTI - Urethral damage leading to clinical significant strictures - Kidney/bladder stone formation - Episodes of macroscopic hematuria	- sUTI (see definition) - sUTI + hospitalization records - sUTI + positive blood culture - Anamnestic - Anamnestic - Anamnestic
Efficiency	X	- Patient satisfaction - Quality of Life (QoL)	- PROMs: ISCQ, InCaSaQ, PGI-I - PROM: EQ-5D-5L

To investigate whether reusable catheters are not less efficient as single use catheters			
Costs-effectiveness To investigate whether reusable catheters are costs-effective in comparison to single use catheters	X	- Quality-adjusted-life-years (QALYs) and incremental costs-effecitiveness ratios (ICER)	- Hospital records - PROMs: iMCQ, iPCQ, EQ-5D-5L
Patient opinions To explore patients opinions on health care costs and environmental burden in the context of CISC	X	- Patient opinion	- Two statement questions answered by a Likert-scale from 1 – 5 (fully agree – fully disagree)

Table 2. Overview of all objectives and outcome measures.

Our hypothesis is that reusable catheters are as safe and efficient as single use catheters and will provide a significant reduction in healthcare costs and medical waste.

Follow up and study procedures

During the baseline visit, patients are randomized to one of the two study arms and baseline characteristics including a urine specimen for urine culture are collected. After the baseline visit, participants have one week to fill in the first questionnaires before the start of the follow-up period (figure 1). The reusable catheters are ordered and delivered at the home of the study participants who are randomized into the intervention arm. After this week, the intervention arm starts with the use of the reusable catheters. One year follow-up will be performed according to the schedule.

Primary outcome measure

The main outcome parameters are symptomatic urinary tract infections (sUTIs). The definition of a sUTI used for this trial is based on the criteria of Woodford et al, on the basis of the EAU guidelines on Neurourology and the NHG Guidelines for Dutch general practitioners (3, 15, 16).

Symptomatic UTI (sUTI): A patient must meet 1 and 2 below:

1. An acute onset of one or more of the following symptoms:
   - dysuria / pain during catheterization
   - Haematuria
   - Urinary frequency

- Urinary urgency
- Suprapubic pain
- Flank pain
- Fever (> 38 ° C)
- Rigors
- Delirium
- In case of a neurogenic bladder: a change in specific symptoms, like increased urinary incontinence, limb spasm and autonomic dysregulation, could be indicative for a sUTI.

2. and one of the following positive diagnostic tests
   - positive urine culture
   - Positive dipslide
   - Positive nitrite test
   - Positive urine sediment

If a study participant has a symptomatic UTI, a urine culture will be performed. Based on this result, antibiotics will be started. If a study participant has consulted their general practitioner for a symptomatic UTI, it is possible that antibiotics were started empirically or based on the results of a recent urine culture. The diagnosis is then to be decided by the local consultant involved in study.

Secondary outcome measures

An overview of all outcome measures is provided in table 2. Other parameters such as patients characteristics, possible changes in urine cultures over time, underlying (immune)diseases, hand function and mobility will be assessed as well.

Secondary safety outcome measures

The following secondary outcome measures are used to investigate the safety of the reusable catheters: the amount of bacteremic UTI (bUTI), hospitalizations due to sUTI, urethral damage

leading to clinical significant strictures, clinical significant kidney- and/or bladder stone formation and episodes of macroscopic hematuria.

Bacteremic UTI (bUTI) is defined as a patient with a sUTI and a blood culture positive for a known uropathogen, providing that their urine culture matches the positive blood culture (in case a urine culture was taken before receiving antibiotics).

Quality of life and patient satisfaction in study participants

Patient satisfaction and QoL in the intervention arm will be analysed by multiple validated patient reported outcome measurements (PROMs) relative to baseline (before start of the reusable catheter) and the control group. The following PROMs will be used: the five level version of the Euroqol 5D (EQ-5D-5L), for assessing QoL (17), the Intermittent Self-Catheterization Questionnaire (ISC-Q), which evaluates QoL in CISC patients, the Intermittent Catheterization Satisfaction Questionnaire (InCaSaQ), which evaluates patient satisfaction in CISC patients(18), and the Patient Global Impression of Improvement (PGI-I) (19). In addition, the SF-Qualiveen, a short-questionnaire measuring urinary specific QoL is used to evaluate urological symptoms (20). All PROMs will be completed at baseline, week 6, 26 and 52.

Patients opinions

Two additional questions concerning patients thoughts on environmental burden and healthcare costs will be asked at baseline and week 52.

Cost-effectiveness analysis

For the purpose of assessing the cost-effectiveness of reusable catheters data will be collected on medical healthcare utilization, productivity losses and QoL of patients alongside the clinical trial. In this cost-effectiveness study, incremental costs and incremental effects of reusable catheters over single use catheters will be assessed, with effects expressed in quality adjusted life-years (QALYs). The cost-effectiveness study will adhere to the Dutch health economic guidelines (21) and will be performed by the institute for Medical Technology Assessment (iMTA) of the Erasmus University in

Rotterdam (EUR). As such the societal perspective will be adopted, meaning that all costs and effects will be included in the analysis, regardless to whom they accrue. The time horizon of the cost-effectiveness study will be equal to the timeframe of the clinical trial. Uncertainty concerning the incremental cost-effectiveness ratios (ICER), QALYs and costs will be assessed using bootstrapping, and this uncertainty will be presented graphically with the CE-acceptability curve. Data on medical healthcare utilization (i.e. volumes) will be collected both through hospital records and by means of the iMTA Medical Consumption Questionnaire (iMCQ) (22). Data on productivity losses will be collected by means of the iMTA Productivity Costs Questionnaire (iPCQ) (23). We will use a willingness to pay (WTP) threshold of €20,000/QALY, based on the reference value for cost-effectiveness determined by the National Health Care Institute of The Netherlands (21). A study on health-economic burden of urinary-catheter-associated infection in England used a similar WTP threshold of £20,000/QALY based on the NICE guidelines (24, 25).

Sample size

The number of studies that have investigated the effects of single use and reusable catheters is limited. Nevertheless, recently Prieto et al. (2015) performed an abridged Cochrane review (26). They reported 8 studies that compared single to reusable catheters. For single use 44 events out of 199 were observed, for reusable 44 events out of 191. This leads to the proportions of 0.22 and 0.23. Further we applied a power of 0.80, a one-sided alpha of 0.025 (it is customary to adjust one-sided alphas to the half of 0.05) and a non-inferiority margin of 50% of the mean proportions; 0.11, as is recommended by Althunian et al. (27). The sample size is then calculated with: $n=((Z(1-a)+Z(1-ß))^2$ [ps (1-ps)+pe (1-pe)])/((ps-pe-d)^2), the formula developed by Blackwelder et al in 1982 (28), leading to 182.4 effective cases in each group. Anticipating a dropout of 20% (29), this must be divided by 80% and rounded upwards. This results in 2 times 228 participants, a total of 456.

Because the lack of comparable non-inferiority designed trials on reusable catheters for CISC with the same primary outcome measurement (sUTI), we chose to look at other non-inferiority trials with a

primary outcome measurement of sUTI in patients on CISC. All these trials handled a non-inferiority marge of 10% (30-34), and two trials even 15% (35, 36). The head researchers and clinicians of the departments of urology and medical microbiology agreed on the 11% marge to be clinical acceptable.

Data collection and management

Data is collected and managed by the (site) researchers in Gemstracker/Limesurvey according to the regulations of the Erasmus MC and the Dutch privacy Law. (Site) investigators will supervise the day-to-day operation of the project and are responsible for ensuring that the Good Clinical Practice guidelines are followed.

Statistical analysis

For analysis of the results, the groups will be stratified for gender and the female patient group will be balanced for pre- and post-menopausal. Data analysis will be performed using SPSS. The primary analysis will be to assess difference between the intervention and the control groups in the sUTI rate using a risk difference and 95% to determine non-superiority. Descriptive statistics will be used to describe baseline characteristics of participating patients in both groups. Binomial of categorical outcome measures will be analysed using Chi-square tests and quantitative outcome variables by t-tests or Mann-Whitney U tests. Two-sides p values are calculated.

Monitoring

Monitoring will be done according to the requirements of the Netherlands Federation of University Medical Centres (NFU) based on the ICH Good Clinical Practice guidelines. Monitoring will be carried out by qualified monitors of the Clinical Trial Center (CTC) of the Erasmus MC. The frequency of complications due to participation in this trial are expected to be low and of low severity and not more often or severe than in the general population. Therefore, the Medical Ethical committee of the Erasmus MC classified this study as a low-risk study. For low-risk clinical trials monitoring will comprise one visit per study site per year.

All adverse events will be registered and classified according to the Common Terminology Criteria for Adverse Events published by the National Institutes of Health of the United States of America (37). In case of a serious adverse event (grade 3 or more), this will be reported to the testing authorities (ToetsingOnline). ToetsingOnline are in control to decide if an early interim analysis is needed to ensure the safety of this trial.

Discussion

Up to now, no randomized controlled trials with sufficient power have been performed to investigate if the use of reusable catheters for CISC is safe and effective in comparison to single use catheters. Only a small number of studies have been performed after the Cochrane analysis of Prieto et al in 2014 (26, 38-41). These studies did not describe whether a proper cleaning technique was used or if the reused catheter was designed for multiple uses. But most of all, no study obtained an adequate sample size to answer the research question. Therefore, the study described in this protocol will add new insights in the use of reusable catheters and provide high-quality evidence if the sample size is achieved (N=456). However, obtaining the sample size might be a pitfall due to following reason: patients who are randomized into the intervention arm need to use the reusable catheter for a year. The reusable catheter is more time consuming due to the preparation measures for safe use. This could potentially result in higher dropout rate in the intervention arm. To minimize the dropout rate, patients are allowed to use a single use catheter in case of emergency. We therefore drafted the following rule to minimize any non-compliance in the intervention group: a maximum of 20% of the catheterizations per week may be performed with a disposable catheter. All study participants in the intervention group will be frequently asked if and how often they used disposable catheters. We chose a maximum of 20% so patients who catheterize 6 times a day are a allowed to use one disposable catheter per day, for example during the night.

Only a rough estimation can be made about catheter consumption and the plastic waste generated by this, because it is unclear how many people are dependent on chronic CISC. A recent study

explored the use of disposable catheters in the Dutch outpatient setting, revealing a prevalence of almost 46,000 chronic and short-term users in 2018 with an expenditure of 74 million euro (7). Extremely high in comparison to the expenditure of indwelling catheters in the Dutch outpatient setting (only 6,7 million euro for 54,000 users) (42). Almost 25% of the users had a neurogenic underlying disease, which are usually chronic users with multiple (4-6) catheterizations per day. Based on this assumption, the amount of disposable catheters used on an annual basis for users with a neurogenic underlying disease is more than 20 million disposable catheters a year. If the Dutch neurogenic bladder population only uses reusable catheters, this number could be reduced considerably annually depending on frequency of replacement of the reusable catheter, which is in Japan once per 6 weeks and in China once per 12 weeks.

If the outcome of this trial leads to a confirmation of non-inferiority of the reusable catheter in comparison to single use catheters, clinical practice will improve and lead to a reduction in health care costs and plastic medical waste in European countries and, ultimately, in the whole world. As a consequence, CISC will also be available in low income countries where the single use catheter at present is much too expensive for the health care system.

Trial status

Currently, the trial is in the recruitment phase.

Declarations

Ethics and dissemination

This study protocol (issue date: 20 September 2019, version 3.0) was reviewed and approved by the Medical Ethics Committee of the Erasmus MC (MEC 2019-0134). All participants will sign the informed consent form before entering the trial. This trial will be performed according to the SPIRIT checklist for non-inferiority trials (see online supplementary file 2). The results of the primary and secondary outcome measurements will be published in an international peer-reviewed journal.

Patient Involvement

Patients, including a patient representative of a relevant patient organization, were involved in the design and conduct of this protocol, including the assessment of the reusable catheter set. During the trial, every patient will be asked to comment on the study and the design of the reusable catheter set.

Author contributions

All authors contributed in the study design. TD and SB contributed equally to this manuscript. JR and BB provided critical revision of the manuscript. TD and BB obtained funding for this trial. All authors approved the final version of the manuscript.

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Competing interests

All authors declare that there are no conflicts of interest.

Data sharing statement

The final trial dataset will be available to study investigators, Steering Committee members and the Research ethic Board at all participating centers. After completion of the trial, the datasets generated and/or analysed will be made available from the senior author on reasonable request.

Compensation of Research Participants

Study participants are reimbursed for the travel costs of four clinical study visits. Each visit is compensated with 20 euros.

Figures:

*Figure 1. Flowchart of screening and follow-up schedule. *UTI symptoms: urinary tract symptoms, QoL: quality of life.*

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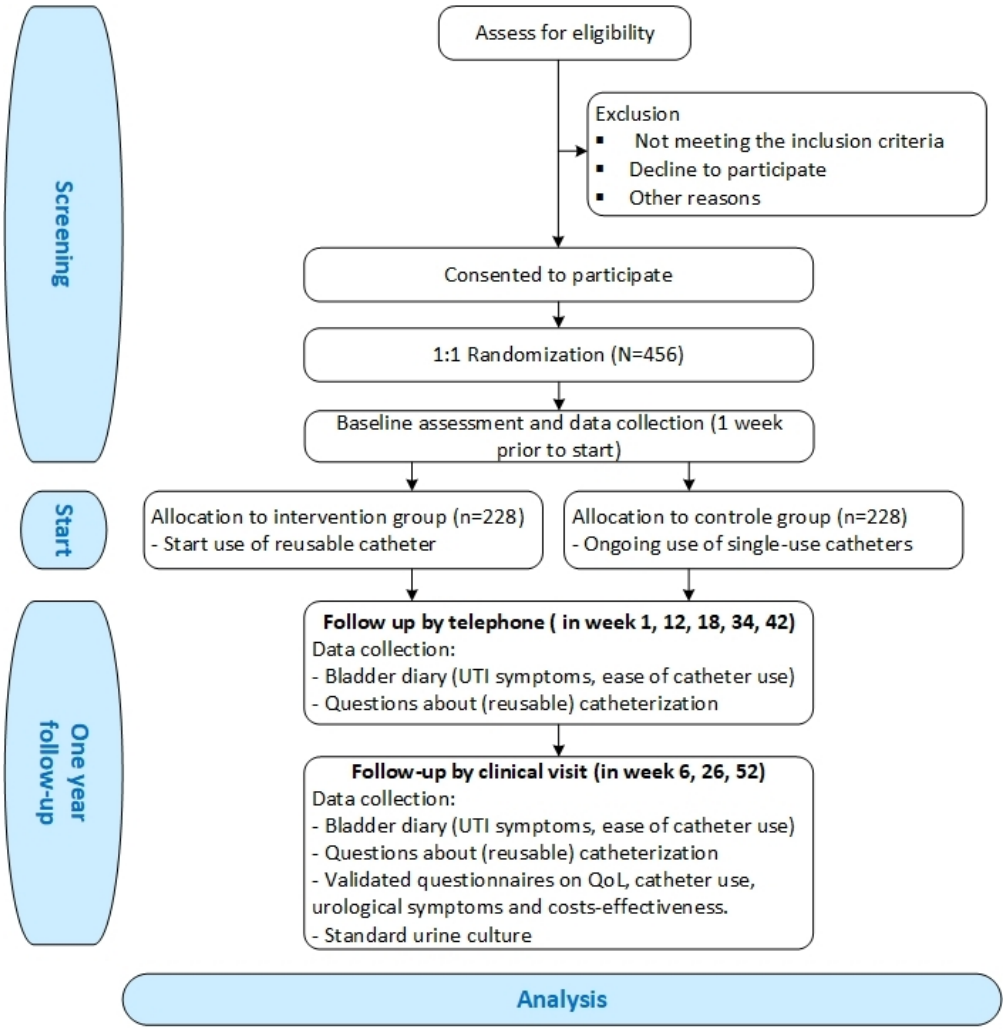

Figure 1. Flowchart of screening and follow-up schedule.

186x190mm (96 x 96 DPI)

Supplementary 1: Subject informed consent form

"The reuse of catheters in patients who catheterize intermittently"

- I have read the information sheet. I was able to ask questions. My questions have been answered well enough. I had enough time to decide if I want to participate.
- I know that taking part is voluntary. I also know that I can decide at any time not to participate or to stop the study. I do not have to explain why.
- I give consent to inform the general practitioner/specialist(s) who treats me that I am participating in this study and that I will potentially use a reusable catheter.
- I give consent to request information from my general practitioner/specialist(s) about the results from urine analysis and side effects.
- I give consent to request information from the laboratory where the urine analyses were performed.
- I give consent to collect and use my data and body material to answer the research question of this study.
- I know that for the monitoring of this research some people can get access to all my data. These people are listed in this information sheet. I give consent for access by these people.

- I give consent to keep my personal information for a period of 15 years and to use it for future research in the field of my condition and/or the investigated treatment method.

  □ **Yes**

  □ **No**

- I give consent to have my body material stored after this study for use in other research, as stated in the information sheet.

  □ **Yes**

  □ **No**

- I give consent to ask me after this study if I want to participate in a follow-up study.

  □ **Yes**

  □ **No**

- I want to participate in this study.

Name of the subject:

Signature: Date : __ / __ / __

I declare that I have fully informed this subject about the above study.

If any information becomes known during the study that could influence the subject's consent, I will let them know in good time.

Investigator name (or their representative):
Signature: Date: __ / __ / __

Additional information was given by:
Name:
Job title:
Signature: Date: __ / __ / __

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* Delete what is not applicable.

The subject will receive a complete information sheet, together with a signed version of the consent form.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1 +2 + 17
Protocol version	3	Date and version identifier	17
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13 + 14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4 + 5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6+7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8 +9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	x
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	x
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10, 11, table 2_
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1.

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	X
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10 - 13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	x

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	x
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	x
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Supl 1
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supl 1
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	18
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	x
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Suppl 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	x

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.